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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,550	06/18/2001	William E. Marshall	P01936US5	1897

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EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 05/30/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/883,550

Applicant(s)

MARSHALL, WILLIAM E.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-22 is/are pending in the application.
- 4a) Of the above claim(s) 20-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 10-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-8 and 10-22 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

The amendment and response filed on 3-17-2003 is acknowledged. Claims 1, 4-8, 10-13, 15 and 17 have been amended. Claim 9 has been canceled. Claims 1-8 and 10-19 are currently under examination.

This application contains claims 20-22 drawn to an invention nonelected with traverse in Paper No. 5. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The declaration by William E. Marshall filed under 37 CFR 1.132 has been fully considered. It should be noted that the attached Figures were unreadable and hence were given no consideration.

Objections Withdrawn

The objection to the specification for failing to properly refer to the parent application is withdrawn in light of the amendment thereto.

The objection of claim 12 for the improper use of the abbreviation SRF is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claim 1 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the use of the phrase "filtering said separated product to remove any stress response products having a molecular weight greater than 10 kDa" is withdrawn in light of the amendment thereto.

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The rejection of claim 1 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the phrase “activating and modulating” is withdrawn. Applicant’s arguments have been fully considered and deemed to be persuasive. Hence, the term “activation” is defined, as per Applicant’s argument, as inducing a monocyte to differentiate into a macrophage. “Modulation” is defined as stimulating the release of IL-1, IL-6 and TNF by macrophages, down-regulating CD-14 receptors and CD-16 receptors on macrophages and preventing the apoptotic death of said macrophages.

The rejection of claim 8 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the use of the phrase “37 C or less” is withdrawn in light of the amendment thereto.

The rejection of claim 10 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the use of the term “stationary phase” is withdrawn in light of the amendment thereto.

The rejection of claim 11 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the use of the phrase “molecular weight cutoff of 10,000” is withdrawn in light of the amendment thereto.

The rejection of claim 12 under 35 U.S.C. 112, second paragraph, for lacking proper antecedent basis for the limitation “the method of claim 1 wherein the filtrate containing SRFs <10kDa...” is withdrawn in light of the amendment thereto.

The rejection of claim 15 under 35 U.S.C. 112, second paragraph as being rendered vague and indefinite by the use of the phrase “having a size of between 0.5 and 3 kDa” is withdrawn in light of the amendment thereto.

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The rejection of claims 1-19 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,840,318 is withdrawn in light of the Terminal Disclaimer filed on 3-17-2003.

The rejection of claims 1-19 under 35 U.S.C. 103(a) as being obvious over Marshall et al. (U.S. Patent 5,840,318) is withdrawn in light of the Declaration by William E Marshall filed under 37 CFR 1.132.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Perdigon et al. (Journal of Food Protection Vol. 53, No. 5, pages 404-410, 1996 – IDS-2) is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 17-19 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase “sequential periods of stress” is maintained for reasons of record.

Applicant argues:

1. The specification clearly states it has “now been found that shorter period of sequential stresses of 20 minutes or less yield more potent SRFs and SRFs of different potencies.

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2. The exact length of time is not as important as being one of a series of washings in aqueous buffers of pH 6.0 to 8.0.

Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear whether the stress factor changes with each successive "period", whether there are rest periods (i.e. removal of stress factors) in between these "periods"? If not, what demarcates the end of one period and the onset of the next? Additionally, claim 18 recites the transferring bacteria to a non-nutritive media and the subsequently transferring the bacteria to non-nutritive media. It is unclear whether this is considered a single "stress period" or multiple periods.

With regard to point 2, it is noted that the features upon which applicant relies (i.e., washings in aqueous buffers of pH 6.0 to 8.0) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1-8 and 10-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al. (Microbiology, Vol. 142, 1996, pages 817-827) is maintained for reasons of record. The cancellation of claim 9 has rendered the rejection of this claim moot.

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Applicant argues:

1. Examiner is misinterpreting Applicant's invention that is not related to bacteriocins.
2. The declaration by Dr. Marshall clearly establishes that the SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties.
3. The results of Figure 1 demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum* and *E. faecium* do not inhibit the growth of *Lactobacillus helveticus*.
4. The bacteriocin Nisin does inhibit the growth of *Lactobacillus helveticus*.
5. Figure 2 shows that stressing *L. monocytogenes* or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bactericidal activity against *L. helveticus*.
6. Figure 3 demonstrates that no bacteriocins against *L. helveticus* are produced by stressing, *L. caseii*, *L. plantarum* or *E. faecium*.
7. Figure 4 shows that the bacteriocin Nisin inhibited 7 strains of bacteria while the SRFs collected from the same strains and *L. caseii* did not inhibit growth.

As outlined previously, De Vuyst et al. disclose methods of producing low molecular weight proteins from bacteria by subjecting them to a number of stresses. By definition, these proteins are stress response factors. These stresses include: a change in temperature, a change in pH, a change in biomass (crowding or decreasing the amount of media), and adding toxins such as ethanol (see abstract). Subjecting the lactic acid bacteria to any of these stressors results in the release of low molecular weight monomers of bacteriocin (approx 6 kDa or less) that

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oligomerize to be about 30 kDa. De Vuyst et al. remove components larger than the bacteriocin monomer (see page 818, column 1). De Vuyst et al. further disclose that these bacteriocins are able to kill or harm other bacterial species and suggest the use of said bacteriocins as food additives (see page 818, column 1). Consequently, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have followed the suggestion of De Vuyst et al. and administer the low molecular weight proteins produced by stressed bacteria to animals since said proteins (bacteriocins) can act to kill or render harmless other strains of bacteria and thereby enhancing the ability of an animal's immune system to deal with bacterial infections minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. Moreover, the internalization of said proteins by an animal would stimulate its the immune system.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced in response to nutrient deprivation.

The rejection of claims 1-8, 10-15 and 17-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Nanji (U.S. Patent 5,413,785 – IDS-2) is maintained for reasons of record. The cancellation of claim 9 has rendered the rejection of this claim moot.

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Applicant argues:

1. There is no suggestion of the claimed invention or the expectation of success in combining the cited references.
2. The cited **reference** does not teach or suggest every element of the claimed invention that must be identically disclosed, in a single reference.
3. It is required that both the suggestion and the expectation of success must be found in prior art. This is not accomplished in regard to De Vuyst et al.
4. SRFs do not directly kill bacteria, as do bacteriocins.
5. Nanji does not reference applicant's SRF that are present in all stressed bacteria.
6. Nanji teaches away from the concept that ordinary lactobacilli that do not inhibit *E. coli* could, when stressed, provide protection against LPS.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 3, De Vuyst et al. disclose methods for producing low molecular weight proteins from stressed bacteria (bacteriocins) and suggests adding said proteins to food (see above). Nanji discloses the administration of lactic acid bacteria to humans, livestock and other animals for protection against endotoxin-mediated shock. Nanji further discloses that said bacteria should be able to produce anti-microbial substances and/or produce proteinaceous antagonistic substances (bacteriocins) since said substances aid in preventing the growth of gram-positive and gram-negative bacteria in the intestine and thereby reducing endotoxin formation (see column 10, lines 40-45). Reduction of endotoxin levels, in turn, reduces the effects of said endotoxin on the immune processes of the animal. Therefore, it would

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have been obvious to one of ordinary skill in the art to use the bacteriocins disclosed by De Vuyst et al. in the treatment methodologies of Nanji in order to take advantage of the immune enhancing effects of the bacteriocins while minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. One would have had a high expectation of success since De Vuyst et al. disclose the use of said bacteriocins as a food additive and Nunji disclose the importance of bacteriocins in reducing endotoxin levels and thereby reducing the deleterious effects of said endotoxin on the animal's immune system.

With regard to Point 2, Applicant is reminded that the rejection was made under 35 U.S.C. 103(a) and not 35 U.S.C. 102. Hence, no single reference needs to disclose all the limitations of the claimed invention since the rejection is based on the combination of the cited references.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention (Points 4 and 6), it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced in response to nutrient deprivation.

With regard to Point 5, the instant claims are not drawn to SRFs that are produce by all stressed bacteria. The instant claims are drawn to **any** factor (protein) produced in response to nutrient deprivation.

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The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Perdigon et al. (Journal of Food Protection Vol. 53, No. 5, pages 404-410, 1996 – IDS-2) is maintained for reasons of record.

Applicant argues:

1. Perdigon teaches that the health benefits of feeding milk fermented with lactobacilli is due to the interaction between the bacteria and the milk solids and that these effects are limited to and based upon the presence of milk.
2. Perdigon teaches away from the use of stressed bacteria alone.

Applicant's arguments have been fully considered and deemed non-persuasive.

Claim 16 is being examined as a method of modulating the immune system of an animal by administering low molecular weight stress proteins as an adjuvant.

The teachings of De Vuyst et al. are discussed above. Perdigon et al. disclose the use of lactic acid bacteria and the proteins produced therein as immunogens and adjuvants in the generation of protection from enteropathogens (see abstract, page 404, column 2 and pages 408-409). It would have been obvious to one of ordinary skill in the art at the time the invention was made to **use the low molecular weight proteins disclosed by De Vuyst et al. as adjuvants** for the induction of a immune response to another co-administered pathogen since Perdigon et al. discusses the use of lactic acid bacteria (and the proteins produced by said bacteria) as adjuvants for enteropathogens (an increased immune response to said enteropathogens was also disclosed) and De Vuyst et al. disclose that proteins produced by lactic acid bacteria have an immunomodulatory effect. Consequently, since the lactic acid bacteria serve as the immunogen,

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they do not need to be separated from the milk in order to meet the limitations of the rejected claim.

New Grounds of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12^{is} rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is rendered vague and indefinite by the use of the phrase “stress response factors (SRFs) <10kDa”. It is unclear what is meant by said term. If applicant is referring to a molecular weight cutoff the phrase “stress response factors (SRFs) with a molecular weight less than 10kDa” is suggested.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
May 28, 2003


LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
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